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Synthesis of deuterated herbicidal ZJ0273, ZJ0702, ZJ0777, and SIOC0163

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ZJ0273 (propyl 4-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamino)benzoate), ZJ0702 (isopropyl 4-(2-(4,6-dimethoxy pyrimidin-2-yloxy)benzylamino)benzoate), ZJ0777 (2-bromo-*N*-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzyl)aniline), and SIOC0163 (5-bromo-*N*-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzyl)pyridin-2-amine) are active ingredients in oilseed rape herbicides. The middle aromatic ring-deuterated form of ZJ0273 was synthesized from ($^2H_6$)phenol and have been successfully used as tracer in its metabolism and degradation study. The methoxyl-deuterated forms of four ingredients were synthesized from ($^2H_4$)methanol, respectively, and they could be used as internal standards in quantitation of herbicide residue in rapeseed and its downstream foodstuff by using HPLC-MS/MS.

Keywords: propyl 4-(2-(4, 6-dimethoxypyrimidin-2-yloxy)benzylamino)benzoate; isopropyl 4-(2-(4, 6-dimethoxypyrimidin-2-yloxy) benzylamino)benzoate; 2-bromo-*N*-(2-(4, 6-dimethoxypyrimidin-2-yloxy)benzyl)aniline; 5-bromo-*N*-(2-(4, 6-dimethoxypyrimidin-2-yloxy)benzyl)pyridin-2-amine; deuterated compounds; synthesis; rape herbicide

Introduction

ZJ0273 (propyl 4-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzyl amino)benzoate), ZJ0702 (isopropyl 4-(2-(4,6-dimethoxy pyrimidin-2-yloxy)benzylamino)benzoate), ZJ0777 (2-bromo-*N*-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzyl)aniline), and SIOC0163 (5-bromo-*N*-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzyl)pyridin-2-amine) are active ingredients in oilseed rape herbicides of 2-pyrimidinyloxy-*N*-arylbenzylamines (Figure 1) co-developed by Shanghai Institute of Organic Chemistry and Zhejiang Institute of Chemical Industry in China.[1,2]

ZJ0273 is a pre-herbicidal ingredient and converts to 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoic acid to work. The ingredient acts on ALS enzyme and belongs to the family of the ALS-inhibitors.[3,4] It is formulated as herbicide under the tradename of Youli (EC) and Youli No.2 (SC) employed on the field.[2] The extractable residues, bound residues, and mineralization of the herbicide in soils meet the non-accumulative criteria of the Commission of the European Communities.[5–7] The only residue of the herbicide in rapeseed is ZJ0273. The residue in rapeseed (1 kg) ranges from 16.97–19.17 μg under simulated field conditions when ZJ0273 is applied at the recommended rate, determined by employing the hyphenated techniques of radioisotope tracing and HPLC-MS.[4] ZJ0702 has equivalent activity and similar herbicidal spectrum as ZJ0273, and its tradename is Youda (EC) and Youhuan (SC). ZJ0777 and SIOC0163, two herbicidal ingredients with low mammalian toxicity and favorable environmental profile, can control many grass weed species as well as broadleaf weeds on rape field. They are individually formulated as herbicides and applied at the rate of 15–90 g of active ingredient/ha at the stage of postemergence.[8,9]

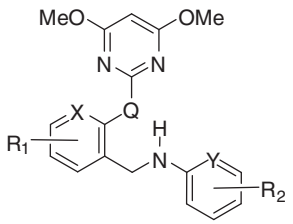

Figure 1. Structures of 2-pyrimidinyloxy-*N*-arylbenzylamines.

With the increase of application amount of these herbicides, growing attentions are paid to the security of rapeseed and its downstream foodstuff, and herbicide residue in rapeseed and its downstream foodstuff gradually become a focused issue on these herbicides. So, it is urgent to develop a method to quantify the residue of these herbicides. Because of high specificity, selectivity, and accuracy, high performance liquid chromatography combined with tandem mass spectrography (HPLC-MS/MS) is a preferable method for this task. A stable isotope-substituted compound is the most ideal internal standard for HPLC-MS/MS analysis.[10] To study the metabolism and degradation of ZJ0273 and to quantify the residue of these herbicides, certain isotope-substituted forms of the herbicidal ingredients are required.

In this paper, we report the synthesis of the middle aromatic ring- and methoxyl-deuterated forms of four herbicidal ingredients.

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Results and discussion

Five deuterated forms of 2-pyrimidinyloxy-*N*-arylbenzylamine herbicidal ingredients were synthesized from ($^2H_6$)phenol in a four-step yield of 44% (**9a**) and from ($^2H_4$)methanol in three-step yields of 49% (**9b**), 51%(**9c**), 46%(**9d**), and 51%(**9e**), respectively, followed by identification by ^1H and ^{13}C NMR, MS(EI), HRMS(EI), UV, and IR.

In the mass spectrum of (**9a**), the *m/z* values of the typical ion fractions (**10a**, **12**, **13**, **14**, Figure 2) are 249, 229, 288, 212 instead of 245, 225, 284, 198 in the spectrum of ZJ0273.[11,12] In the NMR spectrum of (**9a**), the peaks (δ 7.15, 7.31, 7.20, 7.40) corresponding to four hydrogen atoms on the middle aromatic ring of the molecule of ZJ0273 are not observed, and four peaks (δ 122.64, 125.46, 128.12, 128.58) corresponding to four carbon atoms individually split into triple peaks instead of singlet peaks in the NMR spectrum of ZJ0273.[13] These indicate that four deuterium atoms occur on the middle aromatic ring in the molecule of (**9a**). In our downstream study on the metabolism and degradation of ZJ0273 (data not shown), the mixture of ZJ0273, the middle aromatic ring-deuterated form of ZJ0273 (**9a**), and propyl 4-(2-(4,6-dimethoxypyrimidin-2-yloxy)[phenyl-3,4,5,6-$^3H_4$]benzylamino)benzoate (tridium-labeled ZJ0273) was used as a tracer.[14] The tridium-labeled ZJ0273 can effectively discriminate the metabolites and degradation products from the complicated matrix on the basis of radioactivity while it cannot afford molecular structure information. However, (**9a**) in the tracer can provide more molecular structure information based on the relevant isotopic peaks in mass spectrum, which can further validate the structures of the metabolites and degradation products of ZJ0273.

In the NMR spectra of (**9b**), (**9c**), (**9d**), and (**9e**), the peaks (ca. δ 3.79) corresponding to three hydrogen atoms on methoxyl groups in the natural forms of four ingredients all disappear.[11,12] Meanwhile, the peaks (δ 53.63, 53.52, 53.62, 53.65) individually split into heptet peaks due to the C-^2H coupling, compared with the singlet peaks corresponding to carbon atoms on the methoxyl groups in the natural forms of the ingredients. In the mass spectra, the *m/z* values of the typical ion fractions (**10b**, **11,** Figure 2) and accurate molecular weight of (**9b**), (**9c**), (**9d**), and (**9e**) individually shift 6 units from those of their natural forms. These reveal that two trideuteromethoxyl groups present in the molecules of (**9b**), (**9c**), (**9d**), and (**9e**), respectively.

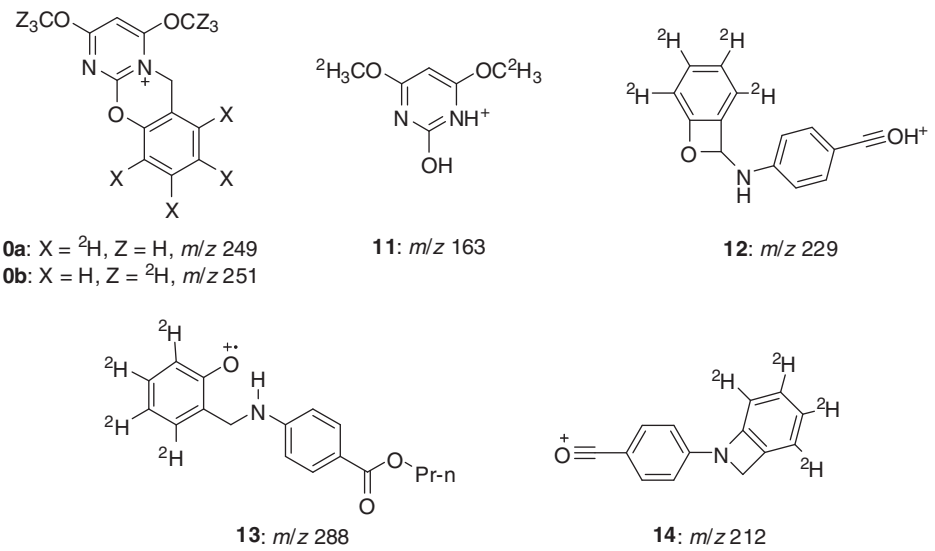
For a deuterated compound used as internal standard in MS analysis, at least three deuterium atoms should be introduced to avoid the possible interference of the isotopic peaks from the natural form of the compound. The deuterium substitution must locate on the specific positions in the compound and deuterium atoms cannot be exchanged in the subsequent study. Moreover, the isotopic purity should be as high as possible.[10]

In the molecule of (**9a**), four deuterium atoms were introduced on the middle aromatic ring. In our previous study on the metabolism and degradation of ZJ0273, the mixture of (**9a**) and ZJ0273 labeled with carbon-14 on the middle ring was employed as a tracer, and the study demonstrated that this deuterated form of ZJ0273 is stable (data not shown). The major metabolites and degradation products of ZJ0273 are 4-(2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamino)benzoic acid and 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoic acid, as means the methoxyl groups are stable.[4] Hence, ZJ0273 was substituted with deuterium atoms on the methoxyl groups, and so were ZJ0702, ZJ0777, and SIOC0163 due to the structural similarities between these three ingredients and ZJ0273. Chemical purities of these deuterated compounds are all greater than 99%, which were determined by HPLC under the conditions as described, employing the natural form of the corresponding standard compounds as external standard, respectively.[11] The mass spectra of the deuterated compounds demonstrates that the isotopic purities are all greater than 99%. Therefore, the methoxyl-deuterated compounds (**9b**), (**9c**), (**9d**), and (**9e**) can be used as internal standards in quantitation of herbicide residue in rapeseed and its downstream foodstuff by employing HPLC-MS/MS.

Experimental

Materials and instruments

($^2H_6$)phenol (D, 99.8%) was purchased from Cambridge Isotope Laboratories (Massachusetts, USA). Anhydrous magnesium dichloride, paraformaldehyde, and ($^2H_4$)methanol (^2H, 99.6%)



10a: X = ^2H, Z = H, *m/z* 249
10b: X = H, Z = ^2H, *m/z* 251

11: *m/z* 163

12: *m/z* 229

13: *m/z* 288

14: *m/z* 212

Figure 2. The typical ion fractions of the deuterated compounds in MS (EI).

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were obtained from Acros Organics (NJ, USA), and methanol for UV spectrum from Fisher Scientific (NJ, USA). Regents were of analytical grade and purchased on market, unless otherwise stated. Flash chromatography was conducted on silica gel (300–400 mesh, Yantai Institute of Chemical Industry, Shandong, China).^{13}C NMR (75 MHz) and ^{1}H NMR (300 MHz) spectra were measured on a Varian 300 spectrometer (Varian Inc., CA, USA) and chemical shifts δwere given in ppm referring to the signal center using the solvent peaks for reference ($CDCl_3$: 7.26/77.36; DMSO-d_6: 2.49/39.7). MS and HRMS spectra were recorded on a 5973N instrument (Agilent Technologies, CA, USA) and a Micromass GCT Premier instrument (Waters Co., MA, USA), respectively. UV analysis was carried out on Cary 100 UV-Vis spectrometer (Varian Inc.) and IR spectra were determined by a Nicolet Avatar 330 FT-IR spectrometer (Thermo Electron Corp., MA, USA). GC-MS analysis was performed on a Varian 4000 GC-MS/MS instrument (Varian Inc.). The melting points were taken on a SGW X-4 microscope melting point instrument without calibration (Shanghai precise science instruments Co., Shanghai, China). HPLC purities of the final deuterated compounds were analyzed by employing Prominence liquid chromatograph system, equipped with SIL-20A auto sampler, LCMS-2010EV mass spectrometer (Shimadzu Co., Kyoto, Japan) and a Diamonsil C_{18} column (5 μm, 4.6 mm × 250 mm, Dikma Technologies, CA, USA). The analysis was performed under the chromatographic conditions as described.[11]

Synthesis section

The deuterated compounds were synthesized from anhydrous ($^{2}H_6$)phenol and ($^{2}H_4$)methanol (Scheme 1) according to the optimized procedures as described, respectively.[11,12,14]

2-Hydroxy(phenyl-3,4,5,6-$^{2}H_4$)benzaldehyde (**2a**)

The mixture of ($^{2}H_6$)phenol (**1**) (10.00 g, 0.10 mol), anhydrous magnesium dichloride (24.24 g, 0.15 mol), anhydrous triethylamine (52 mL, 0.37 mol), and anhydrous acetonitrile (90 mL) was stirred under argon at room temperature for 30 min. Paraformaldehyde (24.24 g, 0.81 mol) was added to the mixture.[12,14] The resulting mixture was refluxed for 4 h and then cooled to room temperature. To the mixture was added 10% HCl (120 mL), followed by extraction with ethyl ether. The combined organic layers were washed with water and saturated brine, dried over anhydrous $MgCl_2$, and evaporated in vacuo to afford colorless oil (**2a**) (10.57 g, 84%). ^{1}H NMR ($CDCl_3$) δ: 9.92 (s, 1H, OH), 11.05 (s, 1H, CHO). GC-MS (EI, 70 eV) *m/z* (%): 126 (M^+, 100), 109(6), 96(27), 69(9).

4,6-Di($^{2}H_3$)methoxy-2-(methylthio)pyrimidine (**4**)

To a two-neck flask containing anhydrous ($^{2}H_4$)methanol (15 mL) at 0–5°C in an ice bath was added a piece of sodium (1.295 g, 56.3 mmol) under argon. The mixture was stirred until it became clear, stirred for another 10 min. The resulting solution was added dropwise to the stirred solution of 4,6-dichloro-2-(methylthio)pyrimidine (**3**) (5.46 g, 28.3 mmol) in anhydrous ($^{2}H_4$)methanol (15 mL) over 10 min and refluxed for 5 h. Water (10 mL) was added into the vigorously stirred reaction mixture, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, purified by flash chromatography (ethyl acetate/petroleum ether 1/200) to afford white powder (**4**) (9.42 g, 85%).^{1}H NMR ($CDCl_3$) δ: 2.52 (s, 3H, SCH_3), 5.70 (s, 1H, CH). HPLC-MS (ESI) *m/z*: 193[M+1]$^+$; ^{13}C NMR ($CDCl_3$) δ: 14.14, 53.40 (hept, ^{1}J = 22.2 Hz, $OC^{2}H_3$), 85.53, 171.06, 171.30. MS (EI, 70 eV) *m/z* (%): 192 (M^+, 100), 146(29), 128(21), 174(18), 69(8), 145(8), 57(6), 194(6). HRMS (EI) calcd for $C_7H_4^2H_6N_2O_2S$ 192.0840, found 192.0837.

4,6-Di($^{2}H_3$)methoxy-2-(methylsulfonyl)pyrimidine (**5b**)

The mixture of (**4**) (4.15 g, 21.8 mmol), sodium tungstate dihydrate (0.2 g, 0.6 mmol) and percarbamide (5.30 g, 44.9 mmol) in acetic acid (15 mL) was stirred at 40°C for 10 min and 50°C for 4 h. To the reaction mixture was added the solution of sodium bisulfite (0.6 M, 20 mL) followed by filtration. The filter cake was recrystallized from ethanol to afford (**5b**) (6.80 g, 68%).[14] ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 3H, SCH_3), 6.15 (s, 1H, CH). ^{13}C NMR ($CDCl_3$) δ: 39.42, 54.82 (hept, ^{1}J = 22.2 Hz, $OC^{2}H_3$), 92.63, 164.91, 173.43. HPLC-MS (ESI) *m/z*: 225 (M^++1). MS (EI, 70 eV) *m/z* (%): 145(100), 224(29), 209(16), 86(13), 146(10), 222(9), 69(9), 93(8). HRMS (EI) calcd for $C_7H_4^2H_6N_2O_4S$ 224.0738, found 224.0739. These data consisted with those of (**5b**) in literature.[15]

General procedure for synthesis of N-arylbenzylideneamines (**7a**)–(**7e**)

To the stirred solution of propyl 4-aminobenzoate (**6a**) (9.89 g, 55.2 mmol) in anhydrous methanol (30 mL) was added 2-hydroxy(*phenyl*-3,4,5,6-$^{2}H_4$)benzaldehyde (**2a**) (6.95 g, 55.1 mmol) at 15–20°C and the stirring was continued for 1 h. Yellow precipitate formed immediately after ca. 30 min. The precipitate was filtered off under vacuum, washed with methanol (10 mL, 0–5°C), and then dried over P_2O_5 under vacuum to afford yellow solid (**7a**). The reaction conditions for the synthesis of (**7d**) were different from those of the other four compounds. The reaction mixture must be refluxed at least 2 h under the catalysis of acetic acid (2–3 drops). These five intermediates were employed without further purification.

General procedure for synthesis of N-arylbenzylamines (**8a**)–(**8e**)

Sodium borohydride (3.20 g, 84 mmol) was added portionwise to the stirred suspension of (**7a**) (12.43 g, 43 mmol) in anhydrous methanol (50 mL) at 0–5°C. The mixture was stirred for 30 min. To the resulting solution was added water (20 mL) then stirred for another 30 min. The solution was concentrated *in vacuo* to remove methanol and extracted with ethyl acetate. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4, and removed solvent under reduced pressure. The resulting residue was recrystallized from ethyl acetate/petroleum ether (1/8) to afford white powder (**8a**).[12]

Propyl 4-(2-hydroxy(phenyl-3,4,5,6-$^{2}H_4$)benzylamino)benzoate (**8a**)

Yield (10.30 g, 82%). m.p. 147–148°C. ^{1}H NMR (DMSO-d_6) δ: 0.92 (t, *J* = 7.2 Hz, 3H, CH_3), 1.65 (m, 2H, CH_2), 4.10 (t, *J* = 6.9 Hz, 2H, OCH_2), 4.27 (s, 2H, NCH), 6.62 (t, *J* = 8.7 Hz, 2H, Ar–H), 7.69 (t, *J* = 8.7 Hz, 2H, Ar–H), 9.56 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 11.06, 22.48, 41.52, 65.65, 111.86, 115.26 (t, *J* = 22.3 Hz, $C^{2}H$), 116.73, 118.98 (t, *J* = 22.3 Hz, $C^{2}H$), 125.41, 127.95(m, $C^{2}H$), 128.50(m, $C^{2}H$), 131.66, 153.55, 155.68, 166.60. MS (EI, 70 eV) *m/z* (%): 120(100), 137(82), 179(52), 289 (M^+, 39), 92(20), 82(20), 111(17), 65(15). HRMS (EI) calcd for $C_{17}H_{15}^2H_4NO_3$ 289.1616, found 289.1614. IR (KBr disk, cm^{-1}) *v*: 3415(s,γ_{N-H}), 1660(s,$\gamma_{C=O}$). UV (MeOH,λ_{max}): 202, 246 nm.

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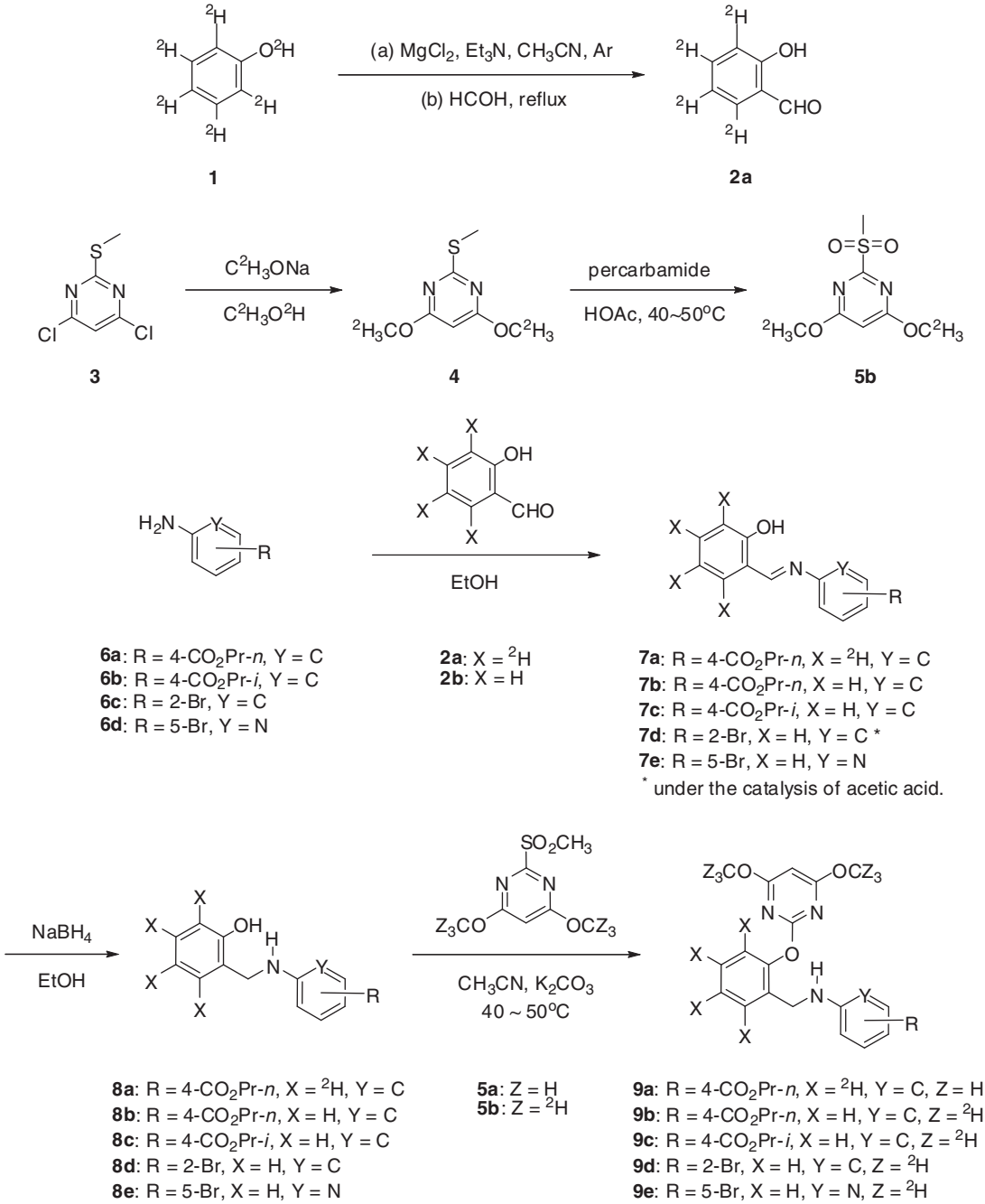

Scheme 1. Synthetic routes of the deuterated compounds.

Propyl 4-(2-hydroxybenzylamino)benzoate (***8b***)

Yield (8.28 g, 83%). ^{1}H NMR (DMSO-d_6) δ: 1.01 (t, J = 7.2 Hz, 3H, CH_3), 1.77 (m, 2H, CH_2, OCH_2), 4.23 (t, J = 6.6 Hz, 2H), 4.43 (s, 2H), 7.91 (d, J = 8.1 Hz, 2H, Ar–H), 6.74 (d, J = 8.1 Hz, 2H, Ar–H), 7.23–7.16 (m, 2H, Ar–H), 6.93–6.84 (m, 2H, Ar–H). MS (EI, 70 eV) *m/z* (%): 120(100), 137(79), 179(43), 285(M^+, 29), 107(21), 78(19), 92(19), 65(17).

Isopropyl 4-(2-hydroxybenzylamino)benzoate (***8c***)

Yield (8.51 g, 87%). ^{1}H NMR ($CDCl_3$) δ: 1.34 (d, J = 6.0 Hz, 6H, CH_3), 4.42 (s, 2H, CH_2), 5.21 (hept, J = 6.0 Hz, 1H, CH), 6.72 (d, J = 8.7 Hz, 2H, Ar–H), 7.89 (d, J = 8.7 Hz, 2H, Ar–H), 6.83–6.93 (m, 2H, Ar–H), 7.14–7.24 (m, 2H, Ar–H). MS (EI, 70 eV) *m/z* (%):137(100), 120(85), 179(62), 285 (M^+, 48), 107(33), 78(19), 121(18), 92(16).

2-((2-Bromophenylamino)methyl)phenol (***8d***)

Yield (5.4 g, 89%). ^{1}H NMR ($CDCl_3$) δ: 4.48 (s, 2H, NCH_2), 6.72–6.81 (m, 1H, Ar–H), 6.85–7.05 (m, 3H, Ar–H), 7.19–7.31 (m, 3H, Ar–H), 7.48–7.55 (m, 1H, Ar–H). MS (EI, 70 eV) *m/z* (%): 171(100), 173(96), 107(27), 77(25), 277 (M^+, 23), 279(23), 65(17), 78(16).

2-((5-Bromopyridin-2-ylamino)methyl)phenol (***8e***)

Yield (4.62 g, 91%). ^{1}H NMR ($CDCl_3$) δ: 4.43 (d, 2H, CNH), 5.20 (brs, 2H, NH), 6.29–6.36 (m, 1H, Ar–H), 6.82–6.97 (m, 2H, Ar–H),

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7.12–7.27 (m, 2H, Ar–H), 7.41–7.46 (m, 1H, Ar–H), 8.09–8.15 (m, 1H, Ar–H). MS (EI, 70 eV) *m/z* (%): 172(100), 174(99), 278 (M^+, 46), 280(45), 77(33), 107(30), 122(26), 78(25).

General procedure for synthesis of deuterated 2-pyrimidinyloxy-N-arylbenzylamines (***9a***)–(***9e***)

To the vigorously stirred solution of propyl 4-(2-hydroxy(*phenyl*-3,4,5,6-$^2H_4$)benzylamino)benzoate (**8a**) (10.13 g, 35 mmol) and 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (**5a**) (7.64 g, 35 mmol) in anhydrous acetonitrile (150 mL) was added anhydrous potassium carbonate (14.51 g, 105 mmol) at 40–50°C. The stirring was continued for 48 h.[12,14] The resulting mixture was filtered and concentrated under vacuum. The residue was subjected to silica gel flash chromatography (ethyl acetate/hexane, 1/8–1/7) to afford (**9a**).[12].

Propyl 4-(2-(4,6-dimethoxypyrimidin-2-yloxy)(phenyl-3,4,5,6-$^2H_4$)benzyl amino)benzoate (***9a***)

Yield (11.89 g, 80%). m.p. 97–98°C. ^{1}H NMR ($CDCl_3$) δ: 1.00 (t, *J* = 7.2 Hz, 3H, CH_3), 1.74 (m, 2H, CH_2), 3.79 (s, 6H, OCH_3), 4.20 (t, *J* = 6.9 Hz, 2H, OCH_2), 4.39 (d, *J* = 5.4 Hz, 2H, NCH_2), 4.68 (t, *J* = 5.4 Hz, 2H, NH), 5.77 (s, 1H, CH), 6.51 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.81 (d, *J* = 8.7 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 10.74, 22.44, 43.07, 54.39, 65.99, 84.64, 111.85, 119.11, 122.64 (t, *J* = 23.9 Hz, C^2H), 125.46 (t, *J* = 23.8 Hz, C^2H), 128.18 (t, *J* = 24.3 Hz, C^2H), 128.58 (t, *J* = 25.1 Hz, C^2H), 130.79, 131.55, 151.19, 151.79, 164.44, 167.06, 173.26. MS (EI, 70 eV) *m/z* (%): 249(100), 427 (M^+, 40), 229(21), 288(17), 212(16), 271(13), 384(4). HRMS (EI) calcd for $C_{23}H^2_{21}H_4O_5N_3$ 427.2045, found 427.2057. IR (KBr disk, cm^{-1}) *v*: 3285(s,γ_{N-H}), 1695(s,$\gamma_{C=O}$), 1595, 1491, 1460(w, w, w,$\gamma_{C=C}$). UV (MeOH,λ_{max}): 203, 247, 304 nm. HPLC purity > 99%.

Propyl 4-(2-(4,6-di($^2H_3$)methoxypyrimidin-2-yloxy)benzylamino) benzoate (***9b***)

Yield (3.25 g, 85%). m.p. 97–98°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (t, *J* = 7.2 Hz, 3H, CH_3), 1.74 (m, 2H, CH_2), 4.18 (t, *J* = 6.9 Hz, 2H, OCH_2), 4.37 (d, *J* = 5.1 Hz, 2H, NCH), 5.76 (s, 1H, CH), 6.47 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.11–7.45 (m, 4H, Ar–H), 7.81 (d, *J* = 8.4 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 173.26, 167.06, 164.45, 151.73, 151.25, 131.57, 130.85, 129.03, 128.73, 125.99, 123.06, 119.17, 111.87, 84.82, 66.02, 53.63 (hept, ^1J = 22.0 Hz, OC^2H_3), 43.16, 22.44, 10.76. MS (EI, 70 eV) *m/z* (%): 251(100), 163(38), 429(M^+, 25), 179(20), 225(20), 284(19), 252(18), 224(16). HRMS(EI) calcd for $C_{23}H^2_{19}H_6N_3O_5$ 429.2171, found 429.2176. IR (KBr disk, cm^{-1}) *v*: 3290(s,γ_{N-H}), 1696(s,$\gamma_{C=O}$), 1540, 1597, 1490 (w, w, w,$\gamma_{C=C}$). UV (MeOH,λ_{max}): 202, 246, 304 nm. HPLC purity >99%.

Isopropyl 4-(2-(4,6-di($^2H_3$)methoxypyrimidin-2-yloxy)benzylamino) benzoate (***9c***)

Yield (1.95 g, 89%). m.p. 83–85°C. ^{1}H NMR ($CDCl_3$) δ: 5.77 (s, 1H, CH), 7.15 (m, H, Ar–H), 7.31 (m, H, Ar–H), 7.20 (m, H, Ar–H), 7.40 (m, H, Ar–H), 4.39 (s, 2H, NCH), 6.49 (d, *J* = 9.0 Hz, 2H, Ar–H), 7.80 (d, *J* = 8.6 Hz, 2H, Ar–H), 5.15 (m, 1H, –CH–); 1.32 (d, *J* = 6.0 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 53.52 (hept, ^1J = 22.3 Hz,OC^2H_3), 173.08, 84.64, 164.24, 151.73, 122.77, 128.54, 125.79, 128.54, 130.03, 42.75, 151.73, 111.58, 29.58, 119.12, 166.38, 67.35, 22.06. MS (EI, 70 eV) *m/z* (%): 251(100), 163(39), 224(29), 225(29), 179(27), 429(M^+, 26), 252(19), 370(15). HRMS (EI) calcd for $C_{23}H^2_{19}H_6N_3O_5$ 429.2171, found 429.2168. IR (KBr disk, cm^{-1}): 3315(s,γ_{N-H}), 1701(s,$\gamma_{C=O}$), 1602, 1488, 1455(w, w, w,$\gamma_{C=O}$). UV (MeOH,λ_{max}): 200, 246, 303 nm. HPLC purity >99%.

2-Bromo-N-(2-(4,6-di($^2H_3$)methoxypyrimidin-2-yloxy)benzyl)aniline (***9d***)

Yield (1.73 g, 79%). m.p. 100–102°C. ^{1}H NMR ($CDCl_3$) δ: 4.43 (s, 2H, NCH_2), 5.79 (s, 1H, CH), 6.47–6.62 (m, 2H, Ar–H), 7.03–7.47 (m, 6H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 173.22, 164.49, 151.24, 144.79, 132.50, 131.09, 128.42, 128.53, 128.49, 125.96, 123.04, 118.01, 111.82, 109.70, 84.90, 53.62 (hept, ^1J = 22.6 Hz, OC^2H_3), 43.32. MS (EI, 70 eV) *m/z* (%): 251(100), 163(38), 260(22), 180(18), 252(18), 261(17), 258(17), 259(17), 421(M^+,11). HRMS (EI) calcd for $C_{19}H_{12}^2H_6BrN_3O_3$ 421.0908, found 421.0904. IR (KBr disk, cm^{-1}): 3415(s,γ_{N-H}), 1599(s,$\gamma_{C=C}$), 1570, 1501, 1515(w, w, w,$\gamma_{C=C}$). UV (MeOH,λ_{max}): 205, 245, 300 nm. HPLC purity > 99%.

5-Bromo-N-(2-(4,6-di($^2H_3$)methoxypyrimidin-2-yloxy)benzyl) pyridin-2-amine (***9e***)

Yield (1.84 g, 88%). m.p. 108–109°C. ^{1}H NMR ($CDCl_3$) δ: 4.45 (s, 2H, NCH_2), 5.38 (brs, 1H, NH), 5.75 (s, 1H, CH), 6.16–6.24 (m, 1H, Ar–H), 7.07–7.44 (m, 5H, Ar–H), 7.95–8.07 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 173.19, 164.33, 157.17, 151.22, 148.31, 139.31, 131.17, 129.19, 128.60, 125.93, 122.89, 106.64, 107.10, 84.76, 53.65 (hept, ^1J = 22.5 Hz, OC^2H_3), 41.68. MS(EI, 70 eV) *m/z* (%): 422(M^+, 100), 424(99), 163(96), 251(91), 261(60), 157(40), 159(39), 259(37). HRMS(EI) calcd for $C_{18}H_{11}^2H_6BrN_4O_3$ 422.0861, found 422.0862. IR (KBr disk, cm^{-1}): 3300(s,γ_{N-H}), 1596(s,$\gamma_{C=C}$), 1575, 1480, 1506 (w, w, w,$\gamma_{C=C}$). UV (MeOH,λ_{max}): 201, 249, 319 nm. HPLC purity > 99%.

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